D4

24. (new) The nucleic acid of Claim 1, wherein the nucleic acid consists of the sequence of SEQ ID NO 15.

II. REMARKS

Claims 1-12, 17, and 19-21 are pending in the subject application. Claims 2, 3, 6 and 9-11 are withdrawn from examination in response to a restriction requirement. Claims 13-16, 18 and 21 have been canceled without prejudice, disclaimer or dedication to the public of any subject matter thereof. Claims 1, 4, 5, 7, 8, 12, 17, and 19-21 stand variously rejected.

By this Amendment, the specification has been amended in response to the Examiner's request. Claims 1, 4, 5, 8, 12, 19, 20, also have been amended and new claims 22 to 24 have been added.

THE AMENDMENTS

The amendments to the claims and the addition of new claims 22 to 24 do not raise an issue of new matter and do not require a further search of the prior art. Claims 19 and 20 have been amended to correct typographical errors. Claim 1 has been amended to delete the term "isolated" and to indicate a guanine at nucleotide position 141. Support for the amendment to the claim is found in Table 3, appearing on page 15 of the specification. The term "isolated" is typically used to distinguish claimed subject matter from the corresponding material as found in nature. Claim 1 as amended is directed to the PB2 gene of a cold-adapted influenza virus. This PB2 gene is not naturally occurring and therefore, claim 1 as amended defines patentable subject matter under 35 U.S.C.

§ 101 (statutory subject matter). This amendment does not affect the scope of the claim 1. Claims 5, 8 and 12 have been amended to delete the term "essentially" and to insert additional sequences coding for reassortant virus (claim 8) and reassortant vaccine (claim 12) further to the Examiner's suggestion. Support for the amendments to claims 8 and 12 can be found throughout the specification, and in particular, on page 5, lines 27-35, Tables 3 and 4 and the sequence listing. Claim 21 has been canceled and substituted by new claims 22 and 23. New claim 24 also has been added. New claim 24 is supported in the specification on page 8, lines 22-25.

Applicants submit that the amendments to the claims were not made earlier since they have been made in response to new grounds of rejection. Entry of the amendments to the specification and claims is respectfully requested.

In view of the preceding amendments and the remarks which follow, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims as set forth below. Amended claims 1, 4, 5, 7, 8, 12, 17, 19, 20 and new claims 22 to 24 presently are under examination.

INFORMATION DISCLOSURE STATEMENT

The Examiner noted that the information disclosure statement filed by Applicants did not comply with the provisions of MPEP 609 because copies of several articles, namely Herlocher et al., abstract of Castrucci, article of Kilbourne and article of WHO, were not received by the Examiner with the PTO 1449 statement.

On June 28, 1995, Applicants' undersigned attorney forwarded to the office copies of the articles as requested by the Examiner. Applicants respectfully

request consideration of the articles and the removal of the outstanding objection to the information disclosure statement.

OBJECTION TO THE SPECIFICATION

The specification is objected to on the ground that accession numbers of the wild type and cold adapted strain are absent from Table I. By this Amendment, Applicants have deleted from the application Table 1 and all reference to the deposited material.

The claims presently under examination refer to specific novel polynucletides, the sequences of which are provided in the SEQ ID listing alone or in combination with polynucleotides having published sequences. Thus, Applicants have provided enablement of the claims without reference to deposited microorganisms. Reconsideration and removal of the objection to the specification is respectfully requested.

35 U.S.C. § 112, FIRST PARAGRAPH

The specification is objected to and the claims stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to adequately teach one of skill in the art how to make/and or use the claimed invention, i.e, for allegedly failing to provide an enabling disclosure for the claimed invention.

The Examiner stated that the elected species of the invention is to reassortant virus containing nucleic acids coding for at least one surface antigen of the wild type virus and the PB2 gene of a cold-adapted virus. The Examiner

argued that the prior art noted that more than the genes coding for PB2 and a surface protein are required for an attenuated vaccine.

Applicants first note that only claim 12 is specifically directed to a vaccine composition. Therefore, in response to the Examiner's rejection but without conceding the correctness of the Examiner's position, claim 12 (and thus its dependents 17, 19 and 20[1]) have been amended to a vaccine comprising polynucleotides coding for the surface proteins HA and NA of a selected wild type influenza virus, polynucleotides coding for PB1, PA and M of a selected cold-adapted influenza virus, and a polynucleotide which consists of the sequence of SEQ ID NO 15 (which codes for PB2). New claim 22 further defines the vaccine. It recites: the vaccine of Claim 12, wherein the polynucleotide coding for M is either of SEQ ID NOS 5 or 7; the polynucleotide coding for PB1 is SEQ ID NO 13; and the polynucleotide coding for PA is SEQ ID NO 11. The amendment to claim 12 removes the ground for rejection and the rejection is not proper against new claim 23.

The Examiner also maintained a separate ground for rejection of the claims under this statutory provision. The Examiner stated that the specification fails to provide guidance to using the elected species reassortant as a vaccine allegedly because Applicants' use of the ferret is insufficient to establish operability of the invention of these claims. The Examiner based his position on the disclosure of Snyder et al. The Examiner opined that Snyder et al. teaches that the ferret is insufficient to predict the efficacy of a cold-adapted, attenuated vaccine. Applicants respectfully traverse.

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[1] Claim 13 previously was canceled without prejudice and therefore will not be addressed.

Claim 12 as amended is directed to a vaccine comprising a reassortant virus, the virus comprising: polynucleotides coding for HA and NA of a selected wild-type influenza virus; polynucleotides coding for PB1, PA, and M of a selected cold-adapted influenza virus; and the gene coding for PB2 shown in SEQ ID NO 15. Claim 17 is directed to the vaccine of claim 12, wherein the wild type influenza virus is from the group listed in Table 8. Claims 19 and 20 are directed to methods of preventing and treating influenza in a patient by introducing an effective amount of the vaccine of claim 12.

First, Applicants note that the work of Snyder et al. appears to be the only contrary opinion to the accepted view that the ferret is the animal model of choice for the study of influenza vaccines.[2] Indeed, evidence of influenza vaccine efficacy in the ferret is accepted by the United States Food and Drug Administration (FDA) for initiation of human clinical trials. Typically, hamsters and mice are used only when the researchers are unable to utilize ferrets because of financial or laboratory constraints or when further statistical support is desired. Mice and hamsters are not considered by Applicants and skilled artisans to be the model of choice because unlike ferrets, these animals do not get flu-like symptoms.

The standard set by the courts for evaluating animal data to support an asserted utility is one of reasonable predictability. In other words, if one skilled in the art would accept the animal tests as being reasonably predictive of utility in

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[2] In support of their position, Applicants direct the Examiner's attention to McLaren and Potter, "Immunity to Influenza in Ferrets" (1974) J. Hyg. Camb. 72:91-100 (a copy of which is enclosed). On page 91; the authors note that "[i]nfluenza in ferrets closely resembles that in man, and the animals are therefore useful as an experimental model in which to study the disease." (citations omitted)

humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility. (See, In re Hartop, 135 U.S.P.Q. 419 (C.C.P.A. 1962). While Snyder et al. suggests that a hamster may be "better" than a ferret model, the reference fails to establish that the ferret is not reasonably predictive of efficacy.

Applicants also direct the Examiner to Subbarao et al. "Rescue of an Influenza A Virus Wild-Type PB2 Gene and a Mutant Derivative Bearing a Site-Specific Temperature-Sensitive and Attenuating Mutation" J. Vir. 67(12):7223-7228 (1993)[3]. Subbarao et al. shows that a synthetic equivalent of the claimed PB2 gene and virus containing the gene exhibited the *ts* and *att* phenotypes. The virus was immunogenic and protected hamsters from subsequent challenge with wild-type virus. The authors conclude that this confirms that these phenotypes are specified by the single amino acid change at position 265 (and corresponding to nucleotide 821). Thus, Applicants have provided evidence of efficacy of the claimed invention in the animal model suggested by the Examiner to be more appropriate than the ferret model.

Accordingly, because Snyder et al. fails to establish that the ferret is not reasonably predictive of clinical outcome, because the ferret is the accepted animal model, and because the claimed invention was shown to be efficacious in the hamster model as suggested by the Examiner, Applicants respectfully request removal of this ground for objection to the specification and rejection of the claims.

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[3] A copy of Subbarao et al. was submitted with Applicants' information disclosure statement even though it is a post filing publication. Nevertheless, a copy of Subbarao et al. is enclosed for the Examiner's convenience.

In view of the preceding amendments and remarks, Applicants respectfully request reconsideration and removal of all grounds for objection to the specification and rejection of the claims under 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 103

Claims 1, 4, 5, 7, 8, 12, 13, 14[4], 17, and 19-21 stand rejected under 35 U.S.C. § 103. Applicants respectfully traverse.

The Examiner admits that the claimed invention is not disclosed or described in the prior art, but maintains the rejection on the ground that it is reasonable to expect that the claimed invention is an obvious or analogous variant of sequences and vaccines disclosed in the prior art since they appear to have the same functional properties.

Applicants again submit that the claims are non-obvious and therefore patentable over the prior art of record. The cited references fail to establish a *prima facie* case of obviousness.

Every pending claim of this application has as an element thereof the PB2 gene manufactured and successfully sequenced by Applicants. The sequence of this gene is provided in SEQ ID NO 15 or 29. No wild type human viruses or reported sequences of cold-adapted viruses have cytosine at position 1933 (SEQ ID NO 15), which the Applicants' note, is believed to be critical to the cold-adapted phenotype:

> "Recent findings indicate that unique structures in influenza viruses may have common regulatory functions. The more stable conformation of the ca molecule predicted by base pairing might

[4] Claims 13 and 14 were previously canceled without prejudice.

> provide a growth advantage over the predicted conformation of the *wt* 2(3) molecule. The importance of RNA structure to biological function has been well documented for poliovirus. The presence of a hairpin structure at the 5' noncoding end has been shown to be necessary for the *ts* phenotype of the virus."

Quoted from page 10, lines 1 to 10 of the specification, citations omitted.

The nucleotide change at position 821 (also present in all pending claims) has been linked to the attenuated and temperature sensitive phenotype of cold-adapted reassortant vaccine. The nucleotide change at 141 may have the same effect as the mutation at position 1933, even though the change is present in a noncoding region.

As noted above, Subbarao et al. further establishes that Applicants' claimed PB2 sequence having guanine at nucleotide 821 (corresponding to a serine rather than asparagine at amino acid position 265) is responsible for the *ts* and *att* phenotypes. All claims currently pending are drawn to a PB2 gene alone or in combination with other genes, wherein the PB2 gene has this attenuating mutation. None of the prior art references, alone or in combination with each other, teaches or suggests that this single nucleotide change (and resulting single amino acid change) would yield a temperature-sensitive and cold-adapted phenotype useful for the production of a vaccine. For this reason, the claims are patentable over the cited prior art.

Specifically, Applicants' PB2 gene differs from the sequence of the gene isolated by Cox et al. at nucleotide positions 714, 963 and 1933. The combination of the prior art fails to teach or suggest the combination of the novel nucleotides at 141, 821 and 1933 which are related to the *ts* and *att* phenotype of the claimed reassortants.

For a reference or combination of references to render obvious a claimed invention, the art must suggest to the skilled artisan the modification between the prior art and the claimed invention. The prior art and the general knowledge available to the skilled artisan reflected in the prior art fail to provide this suggestion or motivation to make the specific modification to arrive at Applicants' invention. There is no suggestion or teaching that the single mutation at position 821 is responsible for a temperature and cold-adapted phenotype. Thus, the cited prior fails to establish a *prima facie* case of obviousness. See In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) (Court held that a *prima facie* case of obviousness was not established. The mere fact that a prior art device could be modified to produce the claimed device does not justify an obviousness rejection unless the prior art suggested the modification's desirability.) For this reason, Applicants submit that the rejection is in error and respectfully request its removal.

Additional support for the patentability of claims having as an element the specific sequence of SEQ ID NO 15 is the additional mutations present at nucleotides 141 and 1933. None of the cited prior art teaches or suggests these mutations or provides the motivation for insertion of additional mutations in the PB2 gene. Indeed, none of the prior art appreciated that multiple mutations within the PB2 gene increases attenuation and temperature sensitivity of a reassortant virus and vaccine having the gene. This has recently been confirmed by another group of investigators. See Subbarao, et al. J. of Virology 69(10):5969-5977 (1995) (copy enclosed) wherein the authors state that sequential introduction of *ts* mutant into the PB2 gene of influenza A/Ann Arbor/6/60 yielded mutants that exhibit a stepwise increase in temperature sensitivity and attenuation as compared with the preceding mutants in the series.

Accordingly, in view of the preceding amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103.

35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 4, 5, 7, 8, 12, 17 and 19-21 are newly rejected for allegedly failing to distinctly claim the subject matter which Applicants regard as the invention. The Examiner objects to use of the term "consisting essentially of" in the claims. Without conceding the correctness of the Examiner's position and without dedication to the public of any subject matter of the claims as filed, Applicants have amended most of the pending claims to recite "consisting of". This amendment was made to expedite prosecution of the claims of this application.

Applicants respectfully submit that the transition term "consisting essentially of" in combination with the remaining elements of the claims adequately defines the scope of the invention and therefore, satisfies 35 U.S.C. § 112, second paragraph. (See Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987), claims need only reasonable apprise those of skill in the art for their scope and be as precise as the subject matter permits to satisfy 35 U.S.C. § 112, second paragraph.) Applicants' claims specifically recite that the sequence must be the same or similar to SEQ ID 15 (claim 1) or SEQ ID 29 (claim 5) and in each case, have guanine at nucleotides 141 and 821 (claim 1 and 5) and cytosine at position 1933 (claim 1 only). Even sequences substantially similar to SEQ ID NOS 15 or 29 must always have guanine at nucleotide positions 141 and 821. This information, in combination

with full disclosure of the PB2 sequence, the biological information in the specification and the level of skill in the art at the time the application was filed, easily informs the public of the content and scope of Applicants' invention. One of skill in the art can easily determine if they are practicing the invention of the claims. Accordingly, this ground for rejection of the claims under 35 U.S.C. § 112, second paragraph is erroneous and Applicants respectfully request its removal.

III. SUMMARY AND CONCLUSION

Applicants believe the subject application is in condition for allowance and respectfully request a notice of allowability. However, if any issues remain, Applicants' undersigned attorney invites the Examiner to telephone her at (415) 813-5730.

In the unlikely event that the transmittal letter is separated from this document and the U.S. Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to our Deposit Account No. 03-1952. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: 13 October 1995

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